```
=> d his 1

     (FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, WPIDS, SCISEARCH, AGRICOLA'
     ENTERED AT 10:10:35 ON 21 DEC 2004)
                SET DUPORDER FILE
L28          33 DUP REM L27 (64 DUPLICATES REMOVED)

=> d que 128
L1          128 SEA LAUGHON A?/AU
L2           21 SEA L1 AND TGF?
L3           24 SEA L1 AND TRANSFORMING(3A) GROWTH(3A) FACTOR#
L4           25 SEA L2 OR L3
L5           20 SEA L4 AND SMAD?
L7            6 SEA L5 AND ?REPRESS?
L8         9867 SEA SMAD
L9          284 SEA DNA(3A) BIND?(5A)(COREPRESS? OR CO(A) REPRESS?)
L10          11 SEA L9 AND SMAD?
L11         225 SEA SMAD?(5A)(COREPRESS? OR CO(A) REPRESS?)
L12         187 SEA L11 AND (BIND? OR INTERACT?)
L13         164 SEA L12 AND (TGF(A) BETA OR TRANSFORMING(3A) GROWTH(3A)
                FACTOR#(A) BETA OR ACTIVIN? OR BMP? OR BONE(3A) MORPHOGEN?)
L14         107 SEA L13 AND REPRESS?(5A) TRANSCRI?
L15          54 SEA L14 AND (ASSAY? OR DETECT? OR IDENTIF? OR MEASUR?)
L17         327 SEA L8 AND BOX?
L18          22 SEA L17 AND (COREPRESS? OR CO(A) REPRESS?)
L19           7 SEA L18 AND CTBP?
L20           6 SEA L18 AND C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?
L21          36 SEA L8 AND (CTBP? OR C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?) AND
                (COREPRES? OR CO(A) REPRESS?) AND (EVI? OR TGIF? OR SIP? OR
                SCHNURRI)
L22         193 SEA L8 AND (DROSOPHILA(3A) MAD? OR MEDEA)
L23         112 SEA L22 AND (ASSAY? OR DETECT? OR IDENTIF? OR MEASUR?)
L24          99 SEA L23 AND (TGF(A) BETA OR TRANSFORMING(3A) GROWTH(3A)
                FACTOR#(A) BETA OR ACTIVIN? OR BMP? OR BONE(3A) MORPHOGEN?)
L25           2 SEA L24 AND (CTBP? OR C(3A) TERMIN?(3A) BIND?(3A) PROTEIN?)
L26           3 SEA L8 AND (DCTBP OR CTBP2 OR CTBP(A) 2)
L27          97 SEA L7 OR L10 OR L15 OR L19 OR L20 OR L21 OR L25 OR L26
L28          33 DUP REM L27 (64 DUPLICATES REMOVED)


=> d ibib abs 128 1-33

L28  ANSWER 1 OF 33     MEDLINE on STN                  DUPLICATE 2
ACCESSION NUMBER:    2003314351     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12714599
TITLE:               Interaction between Smad-interacting protein-1
                     and the corepressor C-terminal
                     binding protein is dispensable for
                     transcriptional repression of E-cadherin.
AUTHOR:              van Grunsven Leo A; Michiels Christine; Van de Putte Tom;
                     Nelles Luc; Wuytens Gunther; Verschueren Kristin;
                     Huylebroeck Danny
CORPORATE SOURCE:    Department of Developmental Biology (VIB7), Flanders
                     Interuniversity Institute for Biotechnology (VIB) and
                     Laboratory of Molecular Biology (Celgen), University of
                     Leuven, Herestraat 49, B-3000 Leuven, Belgium.
SOURCE:              Journal of biological chemistry, (2003 Jul 11) 278 (28)
                     26135-45.
                     Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200308
ENTRY DATE:          Entered STN: 20030708
                     Last Updated on STN: 20030815
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Search done by David Schreiber

Entered Medline: 20030814

AB deltaEF1 and **SIP1** (or Zfhx1a and Zfhx1b, respectively) are the only known members of the vertebrate Zfh1 family of homeodomain/zinc finger-containing proteins. Similar to other transcription factors, both **Smad**-interacting protein-1 (**SIP1**) and deltaEF1 are capable of repressing E-cadherin transcription through binding to the E2 **boxes** located in its promoter. In the case of deltaEF1, this repression has been proposed to occur via interaction with the **corepressor C-terminal binding protein** (**CtBP**). In this study, we show by coimmunoprecipitation that **SIP1** and **CtBP** interact in vivo and that an isolated **CtBP**-binding **SIP1** fragment depends on **CtBP** for transcriptional repression. However, and most importantly, full-length **SIP1** and deltaEF1 proteins do not depend on their interaction with **CtBP** to repress transcription from the E-cadherin promoter. Furthermore, in E-cadherin-positive kidney epithelial cells, the conditional synthesis of mutant **SIP1** that cannot bind to **CtBP** abrogates endogenous E-cadherin expression in a similar way as wild-type **SIP1**. Our results indicate that full-length **SIP1** can repress E-cadherin in a **CtBP** -independent manner.

L28 ANSWER 2 OF 33 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003570374 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14645520
TITLE: **Smad6** recruits **transcription corepressor CtBP** to **repress bone morphogenetic** protein-induced **transcription.**
AUTHOR: Lin Xia; Liang Yao-Yun; Sun Baohua; Liang Min; Shi Yujiang; Brunicardi F Charles; Shi Yang; Feng Xin-Hua
CORPORATE SOURCE: Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, Room 131D, Houston, TX 77030, USA.. xialin@bcm.tmc.edu
CONTRACT NUMBER: F32 GM 70690 (NIGMS)
R01 CA 95731 (NCI)
R01 GM 53874 (NIGMS)
R01 GM 63773 (NIGMS)
SOURCE: Molecular and cellular biology, (2003 Dec) 23 (24) 9081-93. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031216
Last Updated on STN: 20040117
Entered Medline: 20040116

AB Smad6 and Smad7 are inhibitory Smads induced by **transforming growth factor beta-Smad** signal transduction pathways in a negative-feedback mechanism. Previously it has been thought that inhibitory Smads **bind** to the type I receptor and block the phosphorylation of receptor-activated Smads, thereby inhibiting the initiation of **Smad** signaling. Conversely, few studies have suggested the possible nuclear functions of inhibitory Smads. Here, we present compelling **evidence** demonstrating that Smad6 **repressed bone morphogenetic** protein-induced Id1 **transcription** through recruiting transcriptional **corepressor C-terminal binding protein** (**CtBP**). A consensus **CtBP-binding** motif, PLDLS, was **identified** in the linker region of Smad6. Our findings show that mutation in the motif abolished the Smad6 **binding** to **CtBP** and subsequently its **repressor** activity of **transcription**. We conclude that the nuclear functions and physical **interaction** of Smad6 and **CtBP** provide a novel mechanism for the transcriptional regulation

by inhibitory Smads.

L28 ANSWER 3 OF 33 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2003221346 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12743039
TITLE: Regulation of **Smad** signaling through a differential recruitment of coactivators and **corepressors** by ZEB proteins.
AUTHOR: Postigo Antonio A; Depp Jennifer L; Taylor Jennifer J; Kroll Kristen L
CORPORATE SOURCE: Division of Molecular Oncology, Department of Internal Medicine, Washington University School of Medicine, St Louis, MO 63110, USA.. apostigo@im.wustl.edu
SOURCE: EMBO journal, (2003 May 15) 22 (10) 2453-62. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030514
Last Updated on STN: 20030715
Entered Medline: 20030714

AB Balancing signals derived from the TGFbeta family is crucial for regulating cell proliferation and differentiation, and in establishing the embryonic axis during development. TGFbeta/BMP signaling leads to the activation and nuclear translocation of **Smad** proteins, which activate transcription of specific target genes by recruiting P/CAF and p300. The two members of the ZEB family of zinc finger factors (ZEB-1/deltaEF1 and ZEB-2/**SIP1**) regulate TGFbeta/BMP signaling in opposite ways: ZEB-1/deltaEF1 synergizes with **Smad**-mediated transcriptional activation, while ZEB-2/**SIP1** represses it. Here we report that these antagonistic effects by the ZEB proteins arise from the differential recruitment of transcriptional coactivators (p300 and P/CAF) and **corepressors** (**CtBP**) to the Smads. Thus, while ZEB-1/deltaEF1 binds to p300 and promotes the formation of a p300-**Smad** transcriptional complex, ZEB-2/**SIP1** acts as a repressor by recruiting **CtBP**. This model of regulation by ZEB proteins also functions in vivo, where they have opposing effects on the regulation of TGFbeta family-dependent genes during Xenopus development.

L28 ANSWER 4 OF 33 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003159343 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12593671
TITLE: Regulation of TG-**interacting** factor by **transforming growth factor-beta**.
AUTHOR: Chen Feifei; Ogawa Kenji; Nagarajan Raman P; Zhang Meiyu; Kuang Chenzhong; Chen Yan
CORPORATE SOURCE: Department of Medical Molecular Genetics, the Walther Oncology Center, Indiana University School of Medicine, the Walther Cancer Institute, Indianapolis, IN 46202, USA.
CONTRACT NUMBER: R01 DK55991 (NIDDK)
SOURCE: Biochemical journal, (2003 Apr 15) 371 (Pt 2) 257-63. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030406
Last Updated on STN: 20030704
Entered Medline: 20030703

AB TG-**interacting** factor (TGIF) is a **transcriptional co-repressor** that directly associates with **Smad** (Sma- and Mad-related protein) proteins and inhibits Smad-mediated

transcriptional activation. By using Affymetrix (Santa Clara, CA, U.S.A.) oligonucleotide microarray analysis, we found that TGIF mRNA level was elevated by **transforming-growth-factor-beta** (**TGF-beta**) treatment in a human T-cell line, HuT78. Subsequent reverse-transcription PCR **assays** indicated that TGF-beta1 and **activin** were able to induce a rapid and transient increase in the level of TGIF in both HuT78 and HepG2 hepatoma cells. To analyse whether or not the regulation of TGIF mRNA occurs at the transcriptional level, a 2.4 kb human TGIF promoter was isolated. A primer extension **assay** was performed to localize the putative transcription initiation site of the promoter. When transiently expressed in HepG2 cells, this promoter was stimulated by TGF-beta1 and **activin** treatment in a time-dependent manner. A series of deletion mutants of the TGIF promoter were also generated to further characterize the **TGF-beta** responsive region of the promoter. In addition, expression of TGIF was able to cause a dose-dependent inhibition of **TGF-beta** and **activin** signalling. Taken together, these experiments indicated that TGIF is a novel transcriptional target of **TGF-beta** and **activin** signalling and is likely involved in a negative feedback loop to desensitize **TGF-beta/activin** action.

L28 ANSWER 5 OF 33 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2003008596 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12485160
TITLE: Two major Smad pathways in **TGF-beta** superfamily signalling.
AUTHOR: Miyazawa Keiji; Shinozaki Masahiko; Hara Takane; Furuya Toshio; Miyazono Kohei
CORPORATE SOURCE: Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Japan.
SOURCE: Genes to cells : devoted to molecular & cellular mechanisms, (2002 Dec) 7 (12) 1191-204. Ref: 136
Journal code: 9607379. ISSN: 1356-9597.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20030108
Last Updated on STN: 20031218
Entered Medline: 20031217

AB Members of the **transforming growth factor-beta** (**TGF-beta**) superfamily **bind** to two different serine/threonine kinase receptors, i.e. type I and type II receptors. Upon ligand **binding**, type I receptors specifically activate intracellular Smad proteins. R-Smads are direct substrates of type I receptors; Smads 2 and 3 are specifically activated by **activin**/nodal and **TGF-beta** type I receptors, whereas Smads 1, 5 and 8 are activated by **BMP** type I receptors. Nearly 30 proteins have been **identified** as members of the **TGF-beta** superfamily in mammals, and can be classified based on whether they activate **activin/TGF-beta**-specific R-Smads (AR-Smads) or **BMP**-specific R-Smads (BR-Smads). R-Smads form complexes with Co-Smads and translocate into the nucleus, where they regulate the transcription of target genes. AR-Smads **bind** to various proteins, including transcription factors and **transcriptional** co-activators or **co-repressors**, whereas BR-**Smads interact** with other proteins less efficiently than AR-Smads. Id proteins are induced by BR-Smads, and play important roles in exhibiting some biological effects of **BMPs**. Understanding the mechanisms of **TGF-beta** superfamily

signalling is thus important for the development of new ways to treat various clinical diseases in which **TGF-beta** superfamily signalling is involved.

L28 ANSWER 6 OF 33 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001276206 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11278756
TITLE: Ski-interacting protein interacts with **Smad** proteins to augment transforming growth factor-beta-dependent transcription.
AUTHOR: Leong G M; Subramaniam N; Figueroa J; Flanagan J L; Hayman M J; Eisman J A; Kouzmenko A P
CORPORATE SOURCE: Bone & Mineral Research Program, Garvan Institute of Medical Research, Darlinghurst, New South Wales 2010, Australia.. g.leong@garvan.unsw.edu.au
CONTRACT NUMBER: CA28146 (NCI)
CA42573 (NCI)
SOURCE: Journal of biological chemistry, (2001 May 25) 276 (21) 18243-8.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20030105
Entered Medline: 20010705

AB Transforming growth factor-beta (TGF-beta) signaling requires the action of **Smad** proteins in association with other **DNA-binding** factors and coactivator and **corepressor** proteins to modulate target gene transcription. **Smad2** and **Smad3** both associate with the c-Ski and Sno oncoproteins to repress transcription of **Smad** target genes via recruitment of a nuclear corepressor complex. Ski-interacting protein (SKIP), a nuclear hormone receptor coactivator, was examined as a possible modulator of transcriptional regulation of the TGF-beta-responsive promoter from the plasminogen activator inhibitor gene-1. SKIP augmented TGF-beta-dependent transactivation in contrast to Ski/Sno-dependent repression of this reporter. SKIP interacted with **Smad2** and **Smad3** proteins in vivo in yeast and in mammalian cells through a region of SKIP between amino acids 201-333. In vitro, deletion of the Mad homology domain 2 (MH2) domain of **Smad3** abrogated SKIP binding, like Ski/Sno, but the MH2 domain of **Smad3** alone was not sufficient for protein-protein interaction. Overexpression of SKIP partially overcame Ski/Sno-dependent repression, whereas Ski/Sno overexpression attenuated SKIP augmentation of TGF-beta-dependent transcription. Our results suggest a potential mechanism for transcriptional control of TGF-beta signaling that involves the opposing and competitive actions of SKIP and **Smad** MH2-interacting factors, such as Ski and/or Sno. Thus, SKIP appears to modulate both TGF-beta and nuclear hormone receptor signaling pathways.

L28 ANSWER 7 OF 33 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2001276203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11262410
TITLE: **Repression** of dpp targets by binding of brinker to mad sites.
AUTHOR: Kirkpatrick H; Johnson K; **Laughon A**
CORPORATE SOURCE: Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin 53706, USA.
SOURCE: Journal of biological chemistry, (2001 May 25) 276 (21) 18216-22.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20030105
Entered Medline: 20010705

AB Signaling by decapentaplegic (Dpp), a Drosophila member of the **transforming growth factor (TGF)** beta superfamily of growth factors, has recently been shown to activate targets such as vestigial (vg) indirectly through negative regulation of brinker (brk). Here we show that the Brk protein functions as a **repressor** by binding to Dpp response elements. The Brk DNA binding activity was localized to an amino-terminal region containing a putative homeodomain. Brk bound to a Dpp response element of the Ultrabithorax (Ubx) midgut enhancer at a sequence that overlaps a binding site for the **Smad** protein, Mothers Against Dpp (Mad). Furthermore, Brk was able to compete with Mad for occupancy of this binding site. This recognition of overlapping binding sites provides a potential explanation for why the G/C-rich Mad binding site consensus differs the **Smad3/Smad4** binding site consensus. We also found that the Dpp response element from Ubx was more sensitive than the vg quadrant enhancer to **repression** by Brk. This difference correlates with short-range activation of Ubx by Dpp in the visceral mesoderm, whereas vg exhibits a long-range response to Dpp in the wing imaginal disc, indicating that Brk binding sites may play a critical role in limiting thresholds for activation by Dpp. Finally, we provide evidence that Brk is capable of functioning as an active **repressor** . Thus, whereas Brk and Mad compete for regulation of Ubx and vg, Brk may regulate other Dpp targets without direct involvement of Mad.

L28 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 2001340867 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11313276
TITLE: The **corepressor CtBP** interacts with **Evi**-1 to repress transforming growth factor beta signaling.
AUTHOR: Izutsu K; Kurokawa M; Imai Y; Maki K; Mitani K; Hirai H
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Japan.
SOURCE: Blood, (2001 May 1) 97 (9) 2815-22.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB **Evi**-1 is a zinc finger nuclear protein whose inappropriate expression leads to leukemic transformation of hematopoietic cells in mice and humans. This was previously shown to block the antiproliferative effect of transforming growth factor beta (TGF-beta). **Evi**-1 represses TGF-beta signaling by direct interaction with Smad3 through its first zinc finger motif. Here, it is demonstrated that **Evi**-1 represses **Smad**-induced transcription by recruiting **C-terminal binding protein** (**CtBP**) as a **corepressor**. **Evi**-1 associates with **CtBP1** through one of the consensus binding motifs, and this association is required for efficient inhibition of TGF-beta signaling. A specific inhibitor for histone deacetylase (HDAc) alleviates **Evi** -1-mediated repression of TGF-beta signaling, suggesting that HDAc is involved in the transcriptional repression by **Evi**-1. This identifies a novel function of **Evi**-1 as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms for **Evi**-1-induced

leukemogenesis.

L28 ANSWER 9 OF 33 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2001316649 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11389444
TITLE: **TGF-beta** induces assembly of a Smad2-Smurf2 ubiquitin ligase complex that targets SnoN for degradation.
AUTHOR: Bonni S; Wang H R; Causing C G; Kavsak P; Stroschein S L; Luo K; Wrana J L
CORPORATE SOURCE: Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada.
SOURCE: Nature cell biology, (2001 Jun) 3 (6) 587-95.
Journal code: 100890575. ISSN: 1465-7392.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20030304
Entered Medline: 20010920

AB The receptor-regulated Smad proteins are essential intracellular mediators of signal transduction by the **transforming growth factor-beta** (**TGF-beta**) superfamily of growth factors and are also important as regulators of gene transcription. Here we describe a new role for **TGF-beta** -regulated Smad2 and Smad3 as components of a ubiquitin ligase complex. We show that in the presence of **TGF-beta** signalling, Smad2 **interacts** through its proline-rich PPXY motif with the tryptophan-rich WW domains of Smurf2, a recently **identified** E3 ubiquitin ligases. **TGF-beta** also induces the association of Smurf2 with the **transcriptional co-repressor** SnoN and we show that **Smad2** can function to mediate this **interaction**. This allows Smurf2 HECT domain to target SnoN for ubiquitin-mediated degradation by the proteasome. Thus, stimulation by **TGF-beta** can induce the assembly of a Smad2-Smurf2 ubiquitin ligase complex that functions to target substrates for degradation.

L28 ANSWER 10 OF 33 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 2001540678 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11587364
TITLE: Oncogenic mechanisms of **Evi**-1 protein.
AUTHOR: Hirai H; Izutsu K; Kurokawa M; Mitani K
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Hongo, Japan.. hhirai-tky@umin.ac.jp
SOURCE: Cancer chemotherapy and pharmacology, (2001 Aug) 48 Suppl 1 S35-40. Ref: 29
Journal code: 7806519. ISSN: 0344-5704.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20011015
Entered Medline: 20011011

AB Although **Evi**-1 is thought to promote growth or block differentiation in some cell types, its biological functions have not been elucidated. To explore the mechanisms underlying **Evi**-1-induced oncogenesis, we investigated whether **Evi**-1 affects the signaling

of transforming growth factor beta (TGF-beta), which inhibits proliferation of a wide range of cell types and is one of the most studied growth regulatory factors. We demonstrated that **Evi**-1 represses TGF-beta signaling and antagonizes its growth-inhibitory effects. Two separate regions of **Evi**-1 are responsible for this repression, one of which is the first zinc-finger domain. Through this domain, **Evi**-1 physically interacts with Smad3, an intracellular mediator of TGF-beta signaling, thereby suppressing the transcriptional activity of Smad3. These results define a novel function of **Evi**-1 as a repressor of signaling components of TGF-beta. We also demonstrated that **Evi**-1 represses **Smad**-induced transcriptional activation by recruiting **CtBP** as a **corepressor**. **Evi**-1 associates with **CtBP1** through one of the **CtBP**-binding consensus motifs within the region from amino acid 544 to 607, and this association is required for the efficient inhibition of TGF-beta signaling. A specific histone deacetylase (HDAc) inhibitor, trichostatin A (TSA), alleviates **Evi**-1-mediated repression of TGF-beta signaling, suggesting that HDAc is involved in transcriptional repression by **Evi**-1. This identifies a novel function of **Evi**-1 as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms involved in **Evi**-1-induced leukemogenesis. These results indicate that specific HDAc inhibitors may be useful in the treatment of **Evi** -1-induced neoplastic tumors, including myeloid leukemias.

L28 ANSWER 11 OF 33 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 2001106053 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10995736
TITLE: The **interaction** of the carboxyl terminus-**binding** protein with the **Smad corepressor TGIF** is disrupted by a holoprosencephaly mutation in **TGIF**.
AUTHOR: Melhuish T A; Wotton D
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics and Center for Cell Signaling, University of Virginia, Charlottesville, Virginia 22908, USA.
SOURCE: Journal of biological chemistry, (2000 Dec 15) 275 (50) 39762-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The homeodomain protein **TGIF represses transcription** in part by recruiting histone deacetylases. **TGIF binds** directly to DNA to **repress transcription** or **interacts** with **TGF-beta**-activated Smads, thereby repressing genes normally activated by **TGF-beta**. Loss of function mutations in **TGIF** result in holoprosencephaly (HPE) in humans. One HPE mutation in **TGIF** results in a single amino acid substitution in a conserved PLDLS motif within the amino-terminal repression domain. We demonstrate that **TGIF interacts** with the **corepressor** carboxyl terminus-**binding** protein (**CtBP**) via this motif. **CtBP**, which was first **identified** by its ability to **bind** the adenovirus E1A protein, **interacts** both with gene-specific **transcriptional repressors** and with a subset of polycomb proteins. Efficient repression of **TGF-beta**-activated gene responses by **TGIF** is dependent on **interaction** with **CtBP**, and we show that **TGIF** is able to recruit **CtBP** to a **TGF-beta**-activated **Smad**

complex. Disruption of the PLDLS motif in **TGIF** abolishes the **interaction** of **CtBP** with **TGIF** and compromises the ability of **TGIF** to **repress transcription** . Thus, at least one HPE mutation in **TGIF** appears to prevent **CtBP**-dependent **transcriptional repression** by **TGIF**, suggesting an important developmental role for the recruitment of **CtBP** by **TGIF**.

L28 ANSWER 12 OF 33 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 2000283927 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10811875
TITLE: Ski acts as a **co-repressor** with **Smad2** and **Smad3** to regulate the response to type **beta transforming growth factor**.
AUTHOR: Xu W; Angelis K; Danielpour D; Haddad M M; Bischof O; Campisi J; Stavnezer E; Medrano E E
CORPORATE SOURCE: Huffington Center on Aging and Departments of Molecular and Cellular Biology and Dermatology, Baylor College of Medicine and Veterans Affairs Medical Center, Houston, TX 77030, USA.
CONTRACT NUMBER: AG-09990 (NIA)
AG-3663 (NIA)
CA-43600 (NCI)
+
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2000 May 23) 97 (11) 5924-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000630
AB The c-ski protooncogene encodes a transcription factor that **binds** DNA only in association with other proteins. To **identify** co-**binding** proteins, we performed a yeast two-hybrid screen. The results of the screen and subsequent co-immunoprecipitation studies **identified** Smad2 and Smad3, two transcriptional activators that mediate the type **beta transforming growth factor** (**TGF-beta**) response, as Ski-**interacting** proteins. In Ski-transformed cells, all of the Ski protein was found in Smad3-containing complexes that accumulated in the nucleus in the absence of added **TGF-beta**. DNA **binding assays** showed that Ski, Smad2, Smad3, and Smad4 form a complex with the Smad/Ski **binding** element GTCTAGAC (SBE). Ski repressed **TGF-beta**-induced expression of 3TP-Lux, the natural plasminogen activator inhibitor 1 promoter and of reporter genes driven by the SBE and the related CAGA element. In addition, Ski repressed a **TGF-beta**-inducible promoter containing AP-1 (TRE) elements activated by a combination of Smads, Fos, and/or Jun proteins. Ski also repressed synergistic activation of promoters by combinations of Smad proteins but failed to repress in the absence of Smad4. Thus, Ski acts in opposition to **TGF-beta** -induced transcriptional activation by functioning as a **Smad** -dependent **co-repressor**. The biological relevance of this **transcriptional repression** was established by showing that overexpression of Ski abolished **TGF-beta** -mediated growth inhibition in a prostate-derived epithelial cell line.

L28 ANSWER 13 OF 33 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 2000489964 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11041237
TITLE: **TGF-beta**/SMAD signaling and its

involvement in tumor progression.
AUTHOR: Miyazono K
CORPORATE SOURCE: Department of Biochemistry, The Center Institute of the Japanese Foundation for Cancer Research, Tokyo, Japan.. miyazono-ind@umin.ac.jp
SOURCE: Biological & pharmaceutical bulletin, (2000 Oct) 23 (10) 1125-30. Ref: 73
Journal code: 9311984. ISSN: 0918-6158.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB Cytokines of the **transforming growth factor-beta** (**TGF-beta**) superfamily are multifunctional peptides that regulate growth and differentiation of various types of cells. Members of the **TGF-beta** superfamily **bind** to type 11 and type I serine/threonine kinase receptors, which mediate intracellular signals through SMAD proteins. Of 3 subtypes of SMADs, receptor-regulated SMADs are phosphorylated by the serine/threonine kinase receptors, form complexes with common-mediator SMAD, and move into the nucleus, where they act as components of transcription factor complexes. Abnormalities of the **TGF-beta** receptors and SMADs have been **detected** in various tumors, including colorectal cancers and pancreatic cancers. Inhibitory **SMADs** and **transcriptional co-repressors**, including c-Ski and SnoN, repress the **TGF-beta**/SMAD signaling. Perturbation of the **TGF-beta**/SMAD signaling pathway may result in progression of tumors through resistance of the cells to the growth inhibition induced by **TGF-beta**.

L28 ANSWER 14 OF 33 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 2000179494 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10712925
TITLE: **Smads** as transcriptional co-modulators.
AUTHOR: Attisano L; Wrana J L
CORPORATE SOURCE: Department of Anatomy and Cell Biology, University of Toronto, Toronto, M5S 1A8, Canada.. liliana.attisano@utoronto.ca
SOURCE: Current opinion in cell biology, (2000 Apr) 12 (2) 235-43. Ref: 63
Journal code: 8913428. ISSN: 0955-0674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000512

AB The **Smad** signalling pathway is critical for transmitting transforming growth factor-beta (TGF-beta) superfamily signals from the cell surface to the nucleus. In the nucleus, **Smads** regulate transcriptional responses by recruiting co-activators and **co-repressors** to a wide array of **DNA-binding** partners. Thus, **Smads** function as transcriptional co-modulators to regulate TGFbeta-dependent gene expression.

L28 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 2000044797 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10575014
TITLE: c-Ski acts as a **transcriptional** co-**repressor** in **transforming growth factor-beta** signaling through **interaction** with smads.
AUTHOR: Akiyoshi S; Inoue H; Hanai J; Kusanagi K; Nemoto N; Miyazono K; Kawabata M
CORPORATE SOURCE: Department of Biochemistry, The Cancer Institute of Japanese Foundation for Cancer Research, Research for the Future Program, Japan Society for Promotion of Science, 1-37-1, Kami-ikebukuro, Toshima-ku, Tokyo 170-8455, Japan.
SOURCE: Journal of biological chemistry, (1999 Dec 3) 274 (49) 35269-77.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000203
AB Smads are intracellular signaling mediators of the **transforming growth factor-beta** (**TGF-beta**) superfamily that regulates a wide variety of biological processes. Among them, Smads 2 and 3 are activated specifically by **TGF-beta**. We **identified** c-Ski as a Smad2 **interacting** protein. c-Ski is the cellular homologue of the v-ski oncogene product and has been shown to **repress transcription** by recruiting histone deacetylase (HDAC). Smad2/3 **interacts** with c-Ski through its C-terminal MH2 domain in a **TGF-beta**-dependent manner. c-Ski contains two distinct Smad-**binding** sites with different **binding** properties. c-Ski strongly inhibits transactivation of various reporter genes by **TGF-beta**. c-Ski is incorporated in the Smad DNA **binding** complex, interferes with the **interaction** of Smad3 with a transcriptional co-activator, p300, and in turn recruits HDAC. c-Ski is thus a **transcriptional co-repressor** that links **Smads** to HDAC in **TGF-beta** signaling.

L28 ANSWER 16 OF 33 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 1999213492 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10199400
TITLE: A **Smad** transcriptional **corepressor**.
AUTHOR: Wotton D; Lo R S; Lee S; Massague J
CORPORATE SOURCE: Cell Biology Program, Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
CONTRACT NUMBER: CA34610 (NCI)
GM07739 (NIGMS)
SOURCE: Cell, (1999 Apr 2) 97 (1) 29-39.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990427
AB Following TGFbeta receptor-mediated phosphorylation and association with Smad4, Smad2 moves into the nucleus, **binds** to target promoters in association with DNA-**binding** cofactors, and recruits

coactivators such as p300/CBP to activate transcription. We **identified** the homeodomain protein TGIF as a Smad2-**binding** protein and a **repressor** of **transcription**. A TGFbeta-activated Smad complex can recruit TGIF and histone deacetylases (HDACs) to a Smad target promoter, **repressing transcription**. Thus, upon entering the nucleus, a Smad2-Smad4 complex may **interact** with coactivators, forming a transcriptional activation complex, or with TGIF and HDACs, forming a **transcriptional repressor** complex. Formation of one of these two mutually exclusive complexes is determined by the relative levels of **Smad corepressors** and coactivators within the cell.

L28 ANSWER 17 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2001202759 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11226163
TITLE: Epidermal growth factor signaling via Ras controls the **Smad transcriptional co-repressor** TGIF.
AUTHOR: Lo R S; Wotton D; Massague J
CORPORATE SOURCE: Cell Biology Program, Howard Hughes Medical Institute, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA.
SOURCE: EMBO journal, (2001 Jan 15) 20 (1-2) 128-36. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB Smad transcription factors mediate the actions of **transforming growth factor-beta** (**TGF-beta**) cytokines during development and tissue homeostasis. **TGF-beta** receptor-activated Smad2 regulates gene expression by associating with **transcriptional** co-activators or co-**repressors**. The **Smad co-repressor** TGIF competes with the co-activator p300 for Smad2 association, such that TGIF abundance helps determine the outcome of a **TGF-beta** response. Small alterations in the physiological levels of TGIF can have profound effects on human development, as shown by the devastating brain and craniofacial developmental defects in heterozygotes carrying a hypomorphic TGIF mutant allele. Here we show that TGIF levels modulate sensitivity to **TGF-beta**-mediated growth inhibition, that TGIF is a short-lived protein and that epidermal growth factor (EGF) signaling via the Ras-Mek pathway causes the phosphorylation of TGIF at two Erk MAP kinase sites, leading to TGIF stabilization and favoring the formation of **Smad2**-TGIF **co-repressor** complexes in response to **TGF-beta**. These results **identify** the first mechanism for regulating TGIF levels and suggest a potential link for Smad and Ras pathway convergence at the transcriptional level.

L28 ANSWER 18 OF 33 MEDLINE on STN
ACCESSION NUMBER: 2002004558 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11752591
TITLE: Crossing **Smads**.
AUTHOR: Wrana J L
CORPORATE SOURCE: Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, and Department of Medical Genetics and Microbiology, University of Toronto, Canada.. wrana@mshri.on.ca
SOURCE: Science's STKE [electronic resource] : signal transduction knowledge environment, (2000 Mar 14) 2000 (23) RE1. Ref:

69
Journal code: 100964423. ISSN: 1525-8882.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020125
Entered Medline: 20020122

AB The transforming growth factor-beta (TGF-beta) superfamily of secreted polypeptide growth factors exerts extensive control over all aspects of development and homeostasis, and components of this pathway are often mutated in cancers and in several hereditary disorders. Apart from TGF-beta, the superfamily also includes the activins and the bone morphogenetic proteins. These factors signal through heteromeric complexes of type II and type I serine-threonine kinase receptors, which activate the downstream **Smad** signal transduction pathway. Three classes of **Smads** have been defined: the receptor-regulated **Smads** (R-**Smads**), the common-mediator **Smads** (co-**Smads**), and the antagonistic or inhibitory **Smads** (I-**Smads**). Receptor complexes activate the **Smad** pathway by interacting and phosphorylating specific R-**Smads**. Phosphorylation of the R-**Smads** causes dissociation from the receptor and induces assembly into complexes with **Smad4**, a co-**Smad**. This heteromeric complex then translocates into the nucleus, where the **Smads** function as transcriptional comodulators by recruiting coactivators or **corepressors** to **Smad DNA binding** partners. Thus, **Smads** transmit signals directly from the receptor kinase into the nucleus. Crosstalk between **Smads** and other signaling pathways occurs both in the cytosol and in the nucleus. In the cytosol, **Smad** translocation might be inhibited by mitogen-activated protein kinase-dependent phosphorylation, whereas in the nucleus **Smads** interact with a number of transcription factors that themselves are primary targets of other signaling pathways. Furthermore, **Smad** -dependent regulation of these targets often requires input from the primary signaling pathway. In these examples, **Smad** signaling may represent a secondary signal that modifies the output of the primary pathway. Consequently, the transcriptional response to TGF-beta family ligands may be dependent on what other signals are being received by the cell. Crosstalk may thus provide one explanation for the long-standing observation that the biological response to TGF-beta is often dependent on the extracellular environment of the cell.

L28 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:524664 HCAPLUS
DOCUMENT NUMBER: 141:118208
TITLE: Repression of endogenous Smad7 by Ski
AUTHOR(S): Denissova, Natalia G.; Liu, Fang
CORPORATE SOURCE: Ernest Mario School of Pharmacy, Center for Advanced Biotechnology and Medicine and the Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Rutgers, The State Univ. New Jersey, Piscataway, NJ, 08854, USA
SOURCE: Journal of Biological Chemistry (2004), 279(27), 28143-28148
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Ski protein has been proposed to serve as a **corepressor** for **Smad4** to maintain a **transforming growth**

factor-β (TGF-.beta
.)-responsive promoter at a repressed, basal level. However, there have been no reports so far that it indeed acts on a natural promoter. The human Smad7 promoter has been cloned previously, and shown that it contains the 8-base pair palindromic Smad-**binding** element (SBE) necessary for **TGF-β** induction. In this report, the authors have characterized the neg. regulation of Smad7 promoter basal activity by Ski. It was shown that Ski inhibits the Smad7 promoter basal activity in a SBE-dependent manner. Mutation of the SBE abrogates the inhibitory effect of Ski on the Smad7 promoter. Moreover, mutation of the SBE increases the Smad7 promoter basal activity. Using the chromatin immunopptn. **assay**, it was further shown that Ski together with Smad4 **binds** to the endogenous Smad7 promoter. Finally, we show that RNAi knockdown of Ski increases Smad7 reporter gene activity in transient transfection **assays** as well as elevating the endogenous level of Smad7 mRNA. Taken together, our results provide the first evidence that Ski is indeed a **corepressor** for **Smad4**, which can inhibit a natural **TGF-β** responsive gene at the basal state.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:736875 HCAPLUS
DOCUMENT NUMBER: 137:242137
TITLE: Compositions and methods for negative regulation of **TGF-β** pathways
INVENTOR(S): Laughon, Allen S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002137662	A1	20020926	US 2001-810385	20010316
WO 2002076466	A1	20021003	WO 2002-US8133	20020315

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-810385 A 20010316
AB Methods for screening for compds. that are neg. regulators of **TGF-β** -regulated gene expression in mammalian cells are provided, including compns. **identified** therefrom.

L28 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2001:660563 HCAPLUS
DOCUMENT NUMBER: 135:317260
TITLE: **TGIF2** interacts with histone deacetylase 1 and represses transcription
AUTHOR(S): Melhuish, Tiffany A.; Gallo, Christopher M.; Wotton, David
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, 22908, USA
SOURCE: Journal of Biological Chemistry (2001), 276(34), 32109-32114

CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB TG-interacting factor (**TGIF**) is a transcriptional repressor, which represses transcription by binding directly to DNA or interacts with transforming growth factor β (TGFβ)-activated Smads, thereby repressing TGFβ-responsive gene expression. Mutation of **TGIF** in humans causes holoprosencephaly, a severe genetic disorder affecting craniofacial development. Searching human expressed sequence tag data bases revealed the presence of clones encoding a **TGIF**-related protein (**TGIF2**), which contains two regions of high sequence identity with **TGIF**. Here we show that, like **TGIF**, **TGIF2** recruits histone deacetylase, but in contrast to **TGIF**, is unable to interact with the **corepressor CtBP**. **TGIF2** and **TGIF** have very similar DNA-binding homeodomains, and **TGIF2** represses transcription when bound to DNA via a **TGIF** binding site. **TGIF2** interacts with TGFβ-activated Smads and represses TGFβ-responsive transcription. **TGIF2** appears to be a context-independent transcriptional repressor, which can perform similar functions to **TGIF** and may play a role in processes, which, when disrupted by mutations in **TGIF**, cause holoprosencephaly.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:964807 HCAPLUS
DOCUMENT NUMBER: 141:406110
TITLE: Systems and methods for screening for modulators of neural differentiation
INVENTOR(S): Jessel, Thomas; Wichterle, Hynek; Wilson, Sara I.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 55 pp., Cont.-in-part of U.S. Ser. No. 196,882.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224887	A1	20041111	US 2004-789308	20040226
US 2004014210	A1	20040122	US 2002-196882	20020716
PRIORITY APPLN. INFO.:			US 2002-196882	A2 20020716

AB The invention provides in vitro systems for use in identifying modulators of neural differentiation. Also provided are modulators identified by these systems. The invention further provides methods for identifying a modulator of neural differentiation, a modulator of a Wnt signaling pathway, a modulator of Wnt-dependent neural differentiation, a modulator of a BMP signaling pathway, a modulator of BMP-dependent neural differentiation, a modulator of a Hh signaling pathway, and a modulator of Hh-dependent neural differentiation. Also provided are modulators identified by these methods.

L28 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:484254 HCAPLUS
DOCUMENT NUMBER: 141:21226
TITLE: Molecular mechanisms of leukemogenesis by AML1/**EVI-1**
AUTHOR(S): Mitani, Kinuko
CORPORATE SOURCE: Department of Hematology, Dokkyo University School of Medicine, Tochigi, 321-0293, Japan
SOURCE: Oncogene (2004), 23(24), 4263-4269

CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The AML1/**EVI**-1 chimeric gene is generated by the t(3;21)(q26;q22) translocation and plays a pivotal role in progression of hematopoietic stem cell malignancies such as chronic myelocytic leukemia and myelodysplastic syndrome. In AML1/**EVI**-1, an N-terminal half of AML1 including a runt homol. domain is fused to the entire zinc-finger **EVI**-1 protein. AML1 is essential for hematopoietic cell development in fetal liver and its lineage-specific differentiation in adult. In contrast, **EVI**-1 is barely expressed in normal hematopoietic cells, but it is overexpressed in chronic myelocytic leukemia in blastic crisis and myelodysplastic syndrome-derived leukemia. There are at least four mechanisms identified in AML1/**EVI**-1 fusion protein that possibly lead into malignant transformation of hematopoietic stem cells. Firstly, AML1/**EVI**-1 exerts dominant-neg. effects over AML1-induced transcriptional activation. Although target genes repressed by AML1/**EVI**-1 are still not known, binding competition to a specific DNA sequence and histone deacetylase recruitment through a **co-repressor** **CtBP** in **EVI**-1 part are conceivable underlying mechanisms for the dominant-neg. effects. Secondly, AML1/**EVI**-1 interferes with TGFβ signaling and antagonizes the growth-inhibitory effects of TGFβ. The first zinc-finger domain of **EVI**-1 assocs. with Smad3, a TGFβ signal transducer, and represses its transcriptional activity by recruiting histone deacetylase through **CtBP** that interacts with **EVI**-1. Thirdly, AML1/**EVI**-1 blocks JNK activity and prevents stress-induced apoptosis. AML1/**EVI**-1 assocs. with JNK through the first zinc-finger domain of **EVI**-1 and disturbs the association between JNK and its substrates. Lastly, AML1/**EVI**-1 enhances AP-1 activity by activating the c-Fos promoter depending on the second zinc-finger domain of **EVI**-1, and promotes cell proliferation. All these functions cooperatively contribute to the malignant transformation of the hematopoietic stem cells by AML1/**EVI**-1.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:235283 HCAPLUS
DOCUMENT NUMBER: 140:386414
TITLE: **Interaction** with Smad4 is indispensable for suppression of **BMP** signaling by c-Ski
AUTHOR(S): Takeda, Masafumi; Mizuide, Masafumi; Oka, Masako; Watabe, Tetsuro; Inoue, Hirofumi; Suzuki, Hiroyuki; Fujita, Toshiro; Imamura, Takeshi; Miyazono, Kohei; Miyazawa, Keiji
CORPORATE SOURCE: Department of Molecular Pathology and Department of Endocrinology, Graduate School of Medicine, University of Tokyo, Tokyo, 113-0033, Japan
SOURCE: Molecular Biology of the Cell (2004), 15(3), 963-972
CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER: American Society for Cell Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB C-Ski is a transcriptional **corepressor** that **interacts** strongly with **Smad2**, **Smad3**, and Smad4 but only weakly with Smad1 and Smad5. Through **binding** to Smad proteins, c-Ski suppresses signaling of **transforming growth** **factor-β** (**TGF-β**) as well as **bone morphogenetic** proteins (**BMPs**). In the present study, we found that a mutant of c-Ski, termed c-Ski (ARPG) inhibited **TGF-β** /**activin** signaling but not **BMP** signaling. Selectivity was confirmed in luciferase reporter **assays** and by determination of cellular responses in mammalian

cells (**BMP**-induced osteoblastic differentiation of C2C12 cells and **TGF**-β -induced epithelial-to-mesenchymal trans-differentiation of NMuMG cells) and Xenopus embryos. The ARPG mutant recruited histone deacetylases 1 (HDAC1) to the Smad3-Smad4 complex but not to the Smad1/5-Smad4 complex. C-Ski (ARPG) was unable to **interact** with Smad4, and the selective loss of suppression of **BMP** signaling by c-Ski (ARPG) was attributed to the lack of Smad4 **binding**. We also found that c-Ski **interacted** with Smad3 or Smad4 without disrupting Smad3-Smad4 heteromer formation. C-Ski (ARPG) would be useful for selectively suppressing **TGF-.beta** **./activin** signaling.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:304627 HCAPLUS
DOCUMENT NUMBER: 139:95599
TITLE: **Smad4** as a Transcription **Corepressor** for Estrogen Receptor α
AUTHOR(S): Wu, Liyu; Wu, Yalei; Gathings, Bill; Wan, Mei; Li, Xuelin; Grizzle, William; Liu, Zhiyong; Lu, Chongyuan; Mao, Zhengkuan; Cao, Xu
CORPORATE SOURCE: School of Medicine, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, USA
SOURCE: Journal of Biological Chemistry (2003), 278(17), 15192-15200
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antiestrogen compds. exhibit a variety of different effects in different tissues and are widely used for the treatment of osteoporosis, breast cancer, and other diseases. Upon examining the mol. mechanisms, we found that Smad4, a common signal transducer in the **bone morphogenetic** protein (**BMP**)/**transforming growth factor**-β (**TGF**-. **beta**.) signaling pathway, functions as a transcription corepressor for human estrogen receptor α (ERα). Endogenous ERα was co-immunopptd. with Smad4, and the **interaction** was induced by antiestrogen ligands such as tamoxifen, raloxifene, and droloxifen, which was confirmed in chromatin immunopptn. **assays**. Smad4 and ERα form a complex when ERα **binds** to the estrogen-responsive element within the estrogen target gene promoter. Importantly, the expression of Smad4 inhibits both antiestrogen-induced luciferase activity and estrogen downstream target gene transcription in breast cancer cells. Mapping of the **interaction** domains indicates that the activation function 1 (AF1) domain of ERα is essential for its **interaction** with Smad4, while the MH1 domain and linker region of Smad4 are essential for the **interaction**. Our findings represent a novel mechanism that **TGF-.beta** . may regulate cell fate through Smad4-mediated cross-talk with estrogen.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 HCAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.

CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A2	20021210	JP 2002-69354		20020313
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L28 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:223453 HCAPLUS
DOCUMENT NUMBER: 133:145823
TITLE: **Smad6** as a transcriptional **corepressor**
AUTHOR(S): Bai, Shuting; Shi, Xingming; Yang, Xiangli; Cao, Xu
CORPORATE SOURCE: Department of Pathology, University of Alabama School of Medicine, Birmingham, AL, 35294, USA
SOURCE: Journal of Biological Chemistry (2000), 275(12), 8267-8270
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Smad6 and Smad7, a subgroup of Smad proteins, antagonize the signals elicited by **transforming growth factor-beta**.. These two Smads, induced by **transforming growth factor-β** or **bone morphogenetic** protein (**BMP**) stimulation, form stable assocns. with their activated type I receptors, blocking phosphorylation of receptor-regulated Smads in the cytoplasm. Here the authors show that Smad6 **interacts** with homeobox (Hox) c-8 as a transcriptional corepressor, inhibiting **BMP** signaling in the nucleus. The **interaction** between Smad6 and Hoxc-8 was **identified** by a yeast two-hybrid approach and further demonstrated by co-immunopptn. **assays** in cells. Gel shift **assays** show that Smad6, but not Smad7, **interacts** with both Hoxc-8 and Hoxa-9 as a heterodimer when **binding** to DNA. More importantly, the Smad6-Hoxc-8 complex inhibits **interaction** of Smad1 with Hoxc-8- and Smad1-induced transcription activity. These data indicate that Smad6 **interacts** with Hox transcription factors as part of the neg. feedback circuit in the **BMP** signaling pathway.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 28 OF 33 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2001:301470 BIOSIS
DOCUMENT NUMBER: PREV200100301470

TITLE: The **corepressor CTBP** is involved in **Evi**-1 mediated repression of TGF-beta signaling.
AUTHOR(S): Izutsu, Koji [Reprint author]; Kurokawa, Mineo [Reprint author]; Imai, Yoichi [Reprint author]; Mitani, Kinuko [Reprint author]; Hirai, Hisamaru [Reprint author]
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 90a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB **Evi**-1 is a zinc finger nuclear protein whose inappropriate expression leads to leukemic transformation of hematopoietic cells in mice and humans. **Evi**-1 is shown to be highly expressed in human myeloid leukemias and myelodysplastic syndromes by chromosomal rearrangements involving 3q26. It is also aberrantly expressed as a fusion transcript with AML1 (AML1/**Evi**-1), which leads to blastic transformation in patients with chronic myelogenous leukemia. We previously showed that **Evi**-1 and AML1/**Evi**-1 block the antiproliferative effect of TGF-beta. They represses TGF-beta signaling by direct interaction with Smad3 through their first zinc finger motif. Here, we demonstrate that **Evi**-1 represses **Smad**-induced transcription by recruiting **CtBP** as a **corepressor**. **CtBP** was originally identified as a protein which interacts with C-terminal region of adenoviral oncoprotein E1A. **CtBP** is ubiquitously expressed including hematopoietic cells, and has been shown to act as a **corepressor** of certain transcriptional repressors, such as BKLF, FOG, and TCF. We show that **Evi**-1 directly associates with **CtBP1** through one of the consensus binding motifs, and this association is required for efficient inhibition of TGF-beta signaling. A specific inhibitor for histone deacetylase (HDAc) alleviates **Evi**-1-mediated repression of TGF-beta signaling, suggesting that HDAc is involved in the transcriptional repression by **Evi**-1. This identifies a novel function of **Evi**-1 as a member of **corepressor** complexes and suggests that aberrant recruitment of **corepressors** is one of the mechanisms for **Evi**-1-induced leukemogenesis.

L28 ANSWER 29 OF 33 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2000:103749 BIOSIS
DOCUMENT NUMBER: PREV200000103749
TITLE: Multiple modes of repression by the **Smad** transcriptional corepressor TGIF.
AUTHOR(S): Wotton, David; Lo, Roger S.; Swaby, Laurie-Anne C.; Massague, Joan [Reprint author]
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021, USA
SOURCE: Journal of Biological Chemistry, (Dec. 24, 1999) Vol. 274, No. 52, pp. 37105-37110. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Mar 2000
Last Updated on STN: 3 Jan 2002

AB TGIF is a DNA-binding homeodomain protein that has been demonstrated to play a role in transforming growth factor beta-regulated transcription and implicated in the control of retinoid-responsive transcription. We investigated the intrinsic transcriptional activity of TGIF fused to a

heterologous DNA-binding domain. Our results demonstrate that TGIF is a transcriptional repressor able to repress transcription from several different promoters. Repression by TGIF is insensitive to the distance at which it is bound from the promoter. Moreover, the wild type TGIF effectively represses transcription when bound to its cognate DNA-binding site via its homeodomain. Deletion analysis revealed the presence of at least two separable repression domains within TGIF. Repression by one of these is dependent on the activity of histone deacetylases (HDACs), whereas the other appears not to require HDAC activity. Finally, we demonstrate that TGIF interacts with HDACs via its carboxyl-terminal repression domain. Together, these results suggest that TGIF is a multifunctional transcriptional repressor, which acts in part by recruiting HDAC activity.

L28 ANSWER 30 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:445536 SCISEARCH
THE GENUINE ARTICLE: 680BU
TITLE: Opposing functions of ZEB proteins in the regulation of the TGF beta/BMP signaling pathway
AUTHOR: Postigo A A (Reprint)
CORPORATE SOURCE: Washington Univ, Sch Med, Dept Internal Med, Div Mol Oncol, St Louis, MO 63110 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: EMBO JOURNAL, (15 MAY 2003) Vol. 22, No. 10, pp. 2443-2452

Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
ISSN: 0261-4189.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Binding of TGFbeta/BMP factors to their receptors leads to translocation of **Smad** proteins to the nucleus where they activate transcription of target genes. The two-handed zinc finger proteins encoded by Zfhx1a and Zfhx1b, ZEB-1/deltaEF1 and ZEB-2/**SIP1**, respectively, regulate gene expression and differentiation programs in a number of tissues. Here I demonstrate that ZEB proteins are also crucial regulators of TGFbeta/BMP signaling with opposing effects on this pathway. Both ZEB proteins bind to Smads, but while ZEB-1/deltaEF1 synergizes with **Smad** proteins to activate transcription, promote osteoblastic differentiation and induce cell growth arrest, the highly related ZEB-2/**SIP1** protein has the opposite effect. Finally, the ability of TGFbeta to mediate transcription of TGFbeta-dependent genes and induce growth arrest depends on the presence of endogenous ZEB-1/deltaEF1 protein.

L28 ANSWER 31 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:151974 SCISEARCH
THE GENUINE ARTICLE: 643XN
TITLE: Nuclear convergence of the **TGF beta** and cAMP signal transduction pathways in murine embryonic palate mesenchymal cells
AUTHOR: Warner D R (Reprint); Pisano M M; Greene R M
CORPORATE SOURCE: Univ Louisville, Sch Dent, Birth Defects Ctr, Dept Mol Cellular & Craniofacial Biol, 501 S Preston St, Suite 301, Louisville, KY 40292 USA (Reprint); Univ Louisville, Sch Dent, Birth Defects Ctr, Dept Mol Cellular & Craniofacial Biol, Louisville, KY 40292 USA
COUNTRY OF AUTHOR: USA
SOURCE: CELLULAR SIGNALLING, (FEB 2003) Vol. 15, No. 2, pp. 235-242.
Publisher: ELSEVIER SCIENCE INC, 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA.

ISSN: 0898-6568.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Transforming growth factors beta** (TGFbeta) and cyclic AMP (cAMP) both participate in growth and differentiation of the developing mammalian secondary palate and elicit similar biological responses. Cross-talk between these two signal transduction pathways in cells derived from the embryonic palate has been demonstrated previously. In the present study, we have examined nuclear convergence of these signalling pathways at the level of transcriptional complex formation. Biotinylated oligonucleotides encoding a consensus Smad **binding** element (SBE), or a cyclic AMP response element (CRE), were mixed with cell extracts from murine embryonic palate mesenchymal (MEPM) cells that were treated with either TGFbeta or forskolin. Protein-oligonucleotide complexes were precipitated with streptavidin-agarose, and analysed by Western blotting to **identify** proteins in the complex bound to each consensus oligonucleotide. TGFbeta treatment of MEPM cells increased the levels of phosphorylated Smad2, phosphorylated cAMP response element **binding** protein (CREB), and the coactivator, CREB **binding** protein (CBP), that were part of a complex bound to the SBE. Treatment of cells with forskolin, a stimulator of adenylate cyclase, increased the amount of phosphorylated CREB and CBP, but not the amount of phosphorylated Smad2 bound in a complex to the SBE. Additionally, the presence of the co-repressors, c-Ski and SnoN, was demonstrated as part of a complex bound to the SBE (but not the CRE). Amounts of c-Ski and SnoN found in the SBE-containing complex increased in response to either TGFbeta or forskolin. These results demonstrate that phosphorylated CREB forms a complex with the co-activator CBP, phosphorylated **Smad2** and the **co-repressors** c-Ski and SnoN on a consensus SBE. This suggests cooperative regulation of genes with SBE-containing promoters by the cAMP and TGFbeta signalling pathways in the developing palate. (C) 2003 Elsevier Science Inc. All rights reserved.

L28 ANSWER 32 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:600632 SCISEARCH
THE GENUINE ARTICLE: 571XC
TITLE: Overlapping and unique roles for C-terminal binding protein 1 (CtBP1) and **CtBP2** during mouse development.
AUTHOR: Hildebrand J D (Reprint); Soriano P
CORPORATE SOURCE: Univ Pittsburgh, Dept Biol Sci, 5th & Ruskin Ave, Pittsburgh, PA 15260 USA (Reprint); Univ Pittsburgh, Dept Biol Sci, Pittsburgh, PA 15260 USA; Fred Hutchinson Canc Res Ctr, Program Dev Biol, Seattle, WA 98108 USA; Fred Hutchinson Canc Res Ctr, Div Basic Sci, Seattle, WA 98108 USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (AUG 2002) Vol. 22, No. 15, pp. 5296-5307.
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA.
ISSN: 0270-7306.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 52

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The C-terminal binding protein (CtBP) family of proteins has been linked to multiple biological processes through their association with numerous transcription factors. We generated mice harboring mutations in both Ctbp1 and **Ctbp2** to address the in vivo function of CtBPs during vertebrate development. Ctbp1 mutant mice are small but viable and fertile, whereas **Ctbp2**-null mice show defects in axial

patterning and die by E10.5 due to aberrant extraembryonic development. Mice harboring various combinations of Ctbp1 and **Ctbp2** mutant alleles exhibit dosage-sensitive defects in a wide range of developmental processes. The strong genetic interaction, as well as transcription assays with CtBP-deficient cells, indicates that CtBPs have overlapping roles in regulating gene expression. We suggest that the observed phenotypes reflect the large number of transcription factors whose activities are compromised in the absence of CtBP.

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ACCESSION NUMBER: 2000:475743 SCISEARCH
THE GENUINE ARTICLE: 325ZM
TITLE: **TGF-beta** signaling by Smad proteins
AUTHOR: Miyazono K (Reprint)
CORPORATE SOURCE: JAPANESE FDN CANC RES, INST CANC, DEPT BIOCHEM, TOSHIMA KU, 1-37-1 KAMI IKEBUKURO, TOKYO 1708455, JAPAN (Reprint)
COUNTRY OF AUTHOR: JAPAN
SOURCE: CYTOKINE & GROWTH FACTOR REVIEWS, (MAR-JUN 2000) Vol. 11, No. 1-2, pp. 15-22.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 1359-6101.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 42

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Smads are signal transducers for the members of the transforming growth factor-p (TGF-P) superfamily. **Bone morphogenetic** proteins (**BMPs**) and their receptors induce differentiation of C2C12 cells into osteoblast-like cells. Using an adenoviral expression vector system, we showed that receptor-regulated Smads (R-Smads) activated by **BMPs** can induce the differentiation of C2C12 cells. Inhibitory Smads (I-Smads) interfere with the osteoblast differentiation of C2C12 cells by preventing the nuclear translocation of R-Smads. After translocation into the nucleus, Smad oligomers regulate the transcription of target genes through **binding** to DNA directly, **interaction** with other DNA **binding** proteins, and recruitment of **transcriptional** co-activators or co-**repressors**. Through **interaction** with different **transcription** factors and **transcriptional** co-activators or **co-repressors**, **Smads** may exhibit specific effects in various cell types. (C) 2000 Elsevier Science Ltd. All rights reserved.